reconsideration of the restriction. Applicants disagree that the embodiments of Groups I-III fail to have common special feature. The special technical feature is the novel androgens of formula I. Applicants will explain below why the cited prior art fails to render the compounds anticipated or obviousness; and on the other hand, Applicants respectfully submit a 37 C.F.R. §1.132 Declaration showing unexpected results that overcomes the cited 35 U.S.C. §103(a) rejections. Therefore, if claims 1 and 3-11 are patentable, logic dictates that claims 13-16 should also be allowable.

Priority

Applicants acknowledge that the Examiner has reported that **SOME** of the certified copies of the priority documents have been received. Applicants respectfully request the Examiner to identify what copies are present in the file and what copies are not present.

Issue Under 35 U.S.C. §103(a)

Claims 1, and 3-11 stand rejected under 35 U.S.C. §103(a) as being obvious over GB '974 (GB 1298974). Applicants

respectfully submit that patentable distinction exist between the present invention and the cited prior art.

Distinctions Between the Present Invention and GB '974

GB '974 discloses 7β-alkyl steroids and the preparation thereof. GB '974 discloses that the 7 position is substituted with an alkyl group, wherein the alkyl group has from 1 to 10 carbon atoms. As discussed in the April 15, 2002 response, GB' 974 clearly discloses that the 7β configuration is preferred along with an alkyl substitution at the 17 position.

GB '974 fails to disclose or suggest derivatives of 7α-methyl-19-nortestosterone as set forth in the present claims. The Examiner rebutted this argument by stating that an isomer of a prior art compound is obvious without a showing of unexpected results. Applicants traverse this assertion. Stereochemistry cannot be considered obvious. A skilled artisan in organic chemistry would not generally consider a diastereomer as obvious is the synthesis of a compound, especially when one diastereomer is disclosed as preferred.

GB '974 only generally discloses compounds with an alkyl substitution at the 7 position and indicates a preference that leads away from the present compounds by only suggesting "7β-alkylestrones." Applicants assert that a skilled artisan would

not have a reasonable expectation of success of making the present compounds and achieving greater stability *in vivo*, as demonstrated by the longer half-life in the presence of hepatocytes. *See Table on page 26.*

The Examiner must present a *prima facie* case of obviousness consisting of motivation or suggestion to modify or combine references such that one of ordinary skill in the art has a reasonable expectation of success of using the present invention. "To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. In re Rouffet, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998).

As stated above GB '947 fails to provide motivation to a skilled artisan to modify the disclosure to make the present invention as described in the claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Solo et al. discloses a steroid on page 604 where X is OH, Y is H and R is ethyl, nPr and nBu, respectively. The compounds recited by Solo et al appear to have a methyl at the 19 position and the present invention is "19-nortestosterones." The Examiner asserts that a homologue of an "extra methyl group" would be obvious to a skilled artisan.

Applicants assert that the difference between the cited prior art and the present invention is more than a simple homologue. "19-nortestosterone" have different confirmation due to the bulk of the methyl group at the 19 position, and are made through using completely different starting material; thus, it is not a mere alkyl homolog at the 19 position.

Solo et al. only discloses information that 7α-ethyl-testosterone has androgenic activity. In general, testosterone steroids have different activity than 19-nortestosterone

(nandrolone) analogs (see table 3 below) and Solo et al. fails to disclose or suggest the influence of 7α-alkyl substitution for nandrolone.

In the series prepared by Solo et al., the testosterone 7 position methyl analog is said, by reference, to be more potent than testosterone (see page 606, section BIOLOGICAL ACTIVITY). Solo et al fails to disclose that the ethyl analog is more useful than testosterone or MENT. A comparison with MENT is absent and a comparison in TABLE 1, page 607, of higher doses of the ethyl analog (compound 2 in Solo et al) with lower doses of testosterone (compound A in Solo et al) does not suggest any advantage in the ethyl substitution. In fact Solo et al. concludes in the abstract that the testosterone derivatives were found to lose androgenic and anabolic activity rapidly as the size of the group at the 7 position increased. Therefore, the Solo et al. "teaches away" from the present invention.

The Examiner must present a *prima facie* case of obviousness consisting of motivation or suggestion to modify or combine references such that one of ordinary skill in the art has a reasonable expectation of success of making the present invention. "Obviousness can only be established by combining or modifying the teaching of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or

in the knowledge generally available to one of ordinary skill in the art." MPEP 2143.01, *citing* In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Unexpected Results

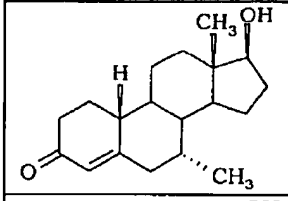
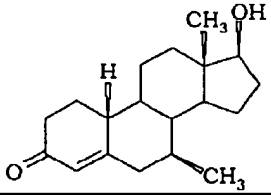
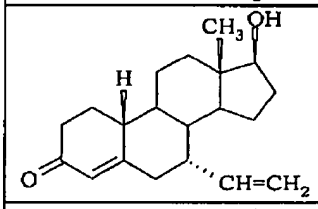
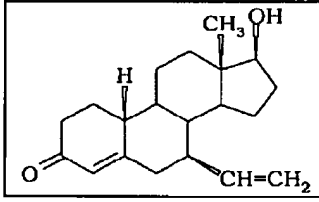
If the Examiner is still not persuaded that a *prima facie* case of obviousness has not been established, Applicants submit the attached 37 C.F.R. §1.132 Declaration by Dr. M.E. De Gooijer.

Regarding GB '974

The submitted data show that a change in the stereochemistry at the 7 position imparts an unexpected change in the effect of the compounds in this field. Inspecting the comparison of MENT with 7β-methyl nandrolone or 7α-vinyl nandrolone with 7β-vinyl nandrolone (Table 1), one can see the major improvement in androgen receptor activation by selecting the 7α stereoconfiguration.

Table 1

A: Androgen receptor activity (data from declaration)

Compound structure	Compound name	A
	7α-methyl nandrolone; 7α-methyl-19-nortestosterone; MENT	269%
	7β-methyl nandrolone	14%
	7α-vinyl nandrolone	190%
	7β-vinyl nandrolone	8%

On top of this, the invention discloses the importance of selection of a substituent length of more than one carbon atom at position 7 of the nandrolone skeleton. This skeleton is also named 19-nortestosterone or 17β-hydroxy-estr-4-en-3-one.

The effect is illustrated by comparison of MENT with 7α-ethyl-nandrolone (Table 2). This is also done in the patent specification on page 25 and 26, wherein Example 1 is 7α-ethyl-

Attorney Docket No. O/99469 US

Issue Under 35 U.S.C. §103(a)

Claims 1, and 3-11 stand rejected under 35 U.S.C. §103(a) as being obvious over Solo et al. (Steroids, Vol, No. 6, pp 603-614). Applicants respectfully submit that patentable distinction exist between the present invention and the cited prior art.

Distinctions Between the Present Invention and Solo et al.

Solo et al. discloses a steroid on page 604 where X is OH, Y is H and R is ethyl, nPr and nBu, respectively. The compounds recited by Solo et al appear to have a methyl at the 19 position and the present invention is "19-nortestosterones." The Examiner asserts that a homologue of an "extra methyl group" would be obvious to a skilled artisan.

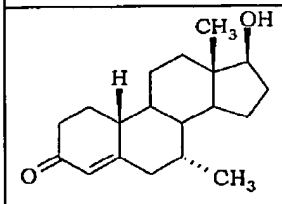
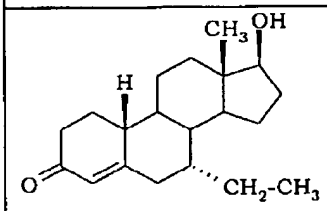
Applicants assert that the difference between the cited prior art and the present invention is more than a simple homologue. "19-nortestosterone" have different confirmation due to the bulk of the methyl group at the 19 position, and are made through using completely different starting material; thus, it is not a mere alkyl homolog at the 19 position.

Solo et al. only discloses information that 7α-ethyl-testosterone has androgenic activity. In general, testosterone steroids have different activity than 19-nortestosterone

nandrolone. Although some activity is lost in the in vitro androgen receptor assay, there is higher activity by oral administration.

Table 2

A: Androgen receptor activity (data from declaration)
B: Metabolic stability $t_{1/2}$ (min) with human hepatocytes (data from specification)
C: ED_{50} in mg/kg p.o. in LH suppression assay (data from specification)

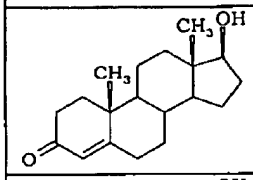
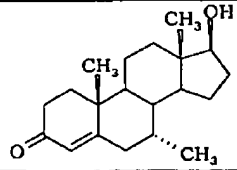
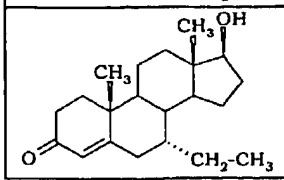
Compound structure	Compound name	*Measurement results*		
		A	*B*	*C*
	7α-methyl nandrolone; MENT; 7α-methyl-19-nortestosterone	269%	20 min	10
	7α-ethyl-nandrolone (7α-ethyl, 17β-hydroxy estr-4-en-3-one)	152%	48 min	2.5

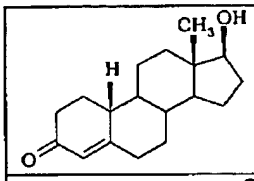
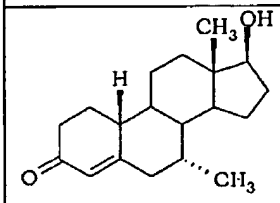
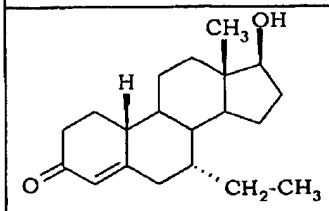
Regarding Solo et al.

Applicants assert that it is well known that testosterone steroids have different activity than 19-nortestosterone (nandrolone) analogs. Thus, a skilled artisan would have no basis for comparison between the testosterone analogs of Solo et al. and the 19-nortestosterone. Thus, the superior results shown in Table 3 and the accompanying §132 declaration would be unexpected to a skilled artisan.

Table 3

A: Androgen receptor activity (data from declaration)
B: Metabolic stability $t_{1/2}$ (min) with human hepatocytes (data from specification supplemented with data from declaration)
C: ED_{50} in mg/kg p.o. in LH suppression assay (data from specification)

Compound structure	Compound name	*Measurement results*		
		A	*B*	*C*
	testosterone	16.5%	15 min	
	7α-methyl-testosterone	45%		
	7α-ethyl-testosterone; Compound 2 in Solo et al	No in house data available		

	nandrolone (19-nortestosterone	55%	16 min	
	7α-methyl nandrolone; MENT; 7α-methyl-19-nortestosterone	269%	20 min	10
	7α-ethyl-nandrolone (7α-ethyl, 17β-hydroxy estr-4-en-3-one)	152%	48 min	2.5

Applicants respectfully request withdrawal of both 35 U.S.C. §103(a) rejection in light of the unexpected results discussed above and in the attached §132 declaration.

Conclusion

Applicants submit that every issue raised by the outstanding Office Action has been addressed and rebutted. Therefore, the present claims define patentable subject matter and are in condition for allowance.

Should the Examiner believe that a conference would be helpful in advancing the prosecution of this application, he is invited to telephone Applicants' Attorney at the number below.

Attorney Docket No. O/99469 US

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attorney Docket No. O/99469 US
MWM

Enclosure: 37 C.F.R. §132 Declaration